? t s5/7/11,13,15,23,24,

5/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015344645 BIOSIS NO.: 200510039145
Pharmacokinetic effects of 4C9, an anti-**FcRn** antibody, in rats: implications for the use of **FcRn inhibitors** for the **treatment** of humoral **autoimmune** and alloimmune conditions
AUTHOR: Getman Kate E; Balthasar Joseph P (Reprint)
AUTHOR ADDRESS: SUNY Buffalo, Dept Pharmaceut Sci, Buffalo, NY 14260 USA** USA
AUTHOR E-MAIL ADDRESS: jb@acsu.buffalo.edu
JOURNAL: Journal of Pharmaceutical Sciences 94 (4): p718-729 APR 05 2005
ISSN: 0022-3549
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: FcRn protects immune gamma globulin (IgG) from intracellular catabolism, and thereby contributes to the long plasma half-life associated with this class of antibody. The present study tested the hypothesis that 4C9, an wanti-FcRn antibody, would increase the in vivo systemic clearance of a model antibody, anti-methotrexate IgG (AMI), in rats. Hybridomas secreting 4C9 and AMI were grown in serum free medium, and monoclonal 4C9 and AMI were purified via protein-G chromatography. Rats were instrumented with jugular vein cannulas 2 - 3 days prior to investigation, and 4C9 was administered intravenously at doses of 3, 15, and 60 mg/kg. AMI was then administered 4, 24, and 48 h after administration of 4C9. Blood samples were collected and assayed to determine AMI concentrations. The anti-FcRn antibody, 4C9, increased AMI systemic clearance in a dose-dependent manner (from 0.99 +/- 0.14 mg/h/kg in control animals to 1.27 +/- 0.05, 1.73 +/- 0.50, and 1.97 +/- 0.49 mL/h/kg in animals treatedwith 3,15, and 60 mg/ kg 4C9; $p < 0.05$). These data were well-captured with an indirect-effect pharmacokinetic-pharmacodynamic model. The effect of 4C9 was found to be transient; no significant effects on AMI systemic clearance were observed when pre-treatment time was increased to 24 or 48 h. As such, the data demonstrate that 4C9, a monoclonal antiFcRn antibody, induces a transient, dose-dependent increase in the elimination of IgG. The results suggest that **FcRn inhibitors** may have utility in the **treatment** of antibodymediated **autoimmune** and alloimmume conditions. (c) 2005 Wiley-Liss, Inc.

5/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015302841 BIOSIS NO.: 200500206643
Fc receptors and their role in immune regulation and **autoimmunity**
AUTHOR: Takai Toshiyuki (Reprint)
AUTHOR ADDRESS: Inst Dev Aging and CancDept Expt Immunol, Japan Sci and Technol Agcy, Seiryo 4-1, Sendai, Miyagi, 9808575, Japan**Japan
AUTHOR E-MAIL ADDRESS: tostakai@idac.tohoku.ac.jp
JOURNAL: Journal of Clinical Immunology 25 (1): p1-18 January 2005 2005
MEDIUM: print
ISSN: 0271-9142
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The activation threshold of cells in the immune system is often tuned by cell surface molecules. The Fc receptors expressed on various hematopoietic cells constitute critical elements for activating or downmodulating immune responses and combines humoral and cell-mediated

immunity. Thus, Fc receptors are the intelligent sensors of the immune status in the individual. However, impaired regulation by Fc receptors will lead to unresponsiveness or hyperreactivity to foreign as well as self-antigens. Murine models for ***autoimmune*** disease indicate the indispensable roles of the inhibitory Fc receptor in the **suppression** of such disorders, whereas activating-type **FcRs** are crucial for the onset and exacerbation of the disease. The development of many **autoimmune** diseases in humans may be caused by impairment of the human Fc receptor regulatory system. This ***review*** is aimed at providing a current overview of the mechanism of Fc receptor-based immune regulation and the possible scenario of how ***autoimmune*** disease might result from their dysfunction.

5/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0015260451 BIOSIS NO.: 200500167187
Identification of FcalphaRI as an **inhibitory** receptor that controls **inflammation**: Dual role of **FcRgamma** ITAM
AUTHOR: Pasquier Benoit; Launay Pierre; Kanamaru Yutaka; Moura Ivan C; Pfirsch Severine; Ruffie Claude; Henin Dominique; Benhamou Marc; Pretolani Marina; Blank Ulrich; Monteiro Renato C (Reprint)
AUTHOR ADDRESS: INSERMU699, Bichat Med Sch, 16 Rue Henri Huchard, F-75870, Paris, 18, France**France
AUTHOR E-MAIL ADDRESS: monteiro@bichat.inserm.fr
JOURNAL: Immunity 22 (1): p31-42 January 2005 2005
MEDIUM: print
ISSN: 1074-7613 (ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Serum IgA is considered a discrete housekeeper of the immune system with multiple anti-**inflammatory** functions, whereas IgA-immune complexes mediate ***inflammatory*** responses. Here, we identify FcalphaRI as a molecular device that determines the nature of IgA responses. In the absence of sustained aggregation, receptor targeting by serum IgA or anti-FalphaRI Fab inhibits activating responses of heterologous FcgammaR or FcepsilonRI. The inhibitory mechanism involves recruitment of tyrosine phosphatase SHP-1 to FcalphaRI and impairment of Syk, LAT, and ERK phosphorylation induced by FcepsilonRI engagement. SHP-1 recruitment is dependent on ERK. Conversely, sustained aggregation of FcalphaRI by multimeric ligands stimulates cell activation by recruiting high amounts of Syk and aborting SHP-1 binding. Both types of signals require the ***FcRgamma*** -ITAM motif. Anti-FcalphaRI Fab **treatment suppresses** manifestations of allergic asthma in FcalphaRI transgenic mice. These findings redefine FcalphaRI as a bifunctional inhibitory/activating receptor of the immune system that mediates both anti- and proinflammatory functions of IgA.

5/7/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014286629 BIOSIS NO.: 200300245348
Essential role of Fcgamma receptors in anti-type II collagen antibody-induced arthritis.
AUTHOR: Kagari Takashi (Reprint); Tanaka Daisuke; Doi Hiromi; Shimozato Takaichi
AUTHOR ADDRESS: Biological Research Laboratories, Sankyo Co., Ltd., 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo, 140-8710, Japan**Japan
AUTHOR E-MAIL ADDRESS: tkagar@shina.sankyo.co.jp
JOURNAL: Journal of Immunology 170 (8): p4318-4324 April 15, 2003 2003
MEDIUM: print

ISSN: 0022-1767 _(ISSN print)
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Anti-type II collagen (anti-CII) Ab is a well-known autoantibody observed in patients with rheumatoid arthritis. Injection of anti-CII Ab and LPS induces arthritis in mice in which anti-CII Ab as well as **inflammatory** cytokines, IL-1beta and TNF-alpha, play critical roles. We investigated the involvement of IgG FcRs (FcgammaRs) in this arthritis model. BALB/c mice injected with the F(ab')2 of anti-CII Ab showed no signs of arthritis. Arthritis development was not observed in **FcRgamma**-/- mice and was partially **suppressed** in FcgammaRIII-/- mice despite the binding of anti-CII Ab and C3 to cartilage surface. Surprisingly, BALB/c mice lacking FcgammaRIIB, which is known as an inhibitory FcgammaR, developed arthritis with no exacerbation in arthritis score compared with wild-type (WT) mice, and only slight exacerbation was observed in the histopathological analysis. In contrast, aged FcgammaRIIB-/- BALB/c mice developed arthritis without LPS injection, suggesting an augmented susceptibility to arthritis in aged FcgammaRIIB-/- mice. No significant difference was observed among BALB/c-WT, -FcRgamma-/-, and -FcgammaRIIB-/- mice on cytokine production induced by anti-CII Ab and LPS injection. Severe arthritis developed in BALB/c-WT and -FcgammaRIIB-/- mice, but not in BALB/c-FcRgamma-/- mice, after the injection of anti-CII Ab and ***inflammatory*** cytokines. These results suggest that the reason behind the nondevelopment of arthritis in FcRgamma-/- BALB/c mice is not due to a disorder in transient cytokine production, but to an irregularity downstream of cytokine production.

5/7/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014270668 BIOSIS NO.: 200300227468
IgG Fc receptor polymorphisms in human disease: Implications for intravenous immunoglobulin therapy.
AUTHOR: Binstadt Bryce A; Geha Raif S; Bonilla Francisco A (Reprint)
AUTHOR ADDRESS: Division of Immunology, Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA**USA
JOURNAL: Journal of Allergy and Clinical Immunology 111 (4): p697-703 April 2003 2003
MEDIUM: print
ISSN: 0091-6749
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Polymorphisms of human Fc receptors (FcRs) have been described that are associated with the development or progression of ***autoimmune*** diseases. The FcR polymorphisms affect the affinity with which ***FcRs*** interact with immunoglobulin molecules. Intravenous immunoglobulin is **administered** as **therapy** for many **autoimmune** diseases and might exert its effects by interacting with ***FcRs*** . Thus, ***FcR*** polymorphisms might influence the efficacy of intravenous immunoglobulin **therapy** for patients with certain ***autoimmune*** diseases. In this article we ***review*** FcR polymorphisms in relation to **autoimmune** diseases for which intravenous immunoglobulin is used therapeutically.
? t s5/7/26,34,40,65,70,77,78,82,84,86,88,94,115,119

5/7/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014233735 BIOSIS NO.: 200300192454

Novel low affinity Fc receptor ligands (**FcRLs**) **suppress** experimental ***autoimmune*** encephalomyelitis (EAE).
AUTHOR: Jensen Mark A (Reprint); White David M (Reprint); Arnason Barry G W (Reprint)
AUTHOR ADDRESS: Chicago, IL, USA**USA
JOURNAL: Neurology 60 (5 Supplement 1): pA223 March 11, 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 55th Annual Meeting of the American Academy of Neurology Honolulu, Hawaii, USA March 29-April 05, 2003; 20030329
ISSN: 0028-3878 _(ISSN print)
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English

5/7/34 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0013591901 BIOSIS NO.: 200200185412
Fc receptors are critical for **autoimmune inflammatory** damage to the central nervous system in experimental **autoimmune** encephalomyelitis
AUTHOR: Abdul-Majid K-B (Reprint); Stefferl A; Bourquin C; Lassmann H; Linington C; Olsson T; Kleinau S; Harris R A
AUTHOR ADDRESS: Neuroimmunology Unit, Center for Molecular Medicine, Karolinska Hospital, L8:04, SE-17176, Stockholm, Sweden**Sweden
JOURNAL: Scandinavian Journal of Immunology 55 (1): p70-81 January, 2002 2002
MEDIUM: print
ISSN: 0300-9475
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Multiple sclerosis (MS) is simulated by various forms of experimental **autoimmune** encephalomyelitis, in which T cells, antibodies, cytokines and complementary factors interact with the central nervous system (CNS) myelin proteins and lead to **inflammatory** damage. We investigated the role of Fc receptors (FcRs), which link the cellular and humoral branches of the immune system, in myelin oligodendrocyte glycoprotein (MOG)-induced experimental **autoimmune** encephalomyelitis (EAE), using two different FcRgamma knockout DBA/1 mice. The first knockout were the FcRgamma chain-deficient mice, which lack FcgammaRI, FcgammaRIII and FcepsilonRI, while the second knockout mice lack only FcgammaRII. The lack of FcgammaRII enhanced the disease susceptibility with associated increased CNS demyelination. While FcRgamma+/+ DBA/1 mice also developed pronounced CNS infiltration and myelin destruction, FcRgamma-/- littermates were protected despite initial peripheral ***autoimmune*** responses to MOG. In vitro analyses revealed equivalent potentials of fluid phase phagocytosis of myelin and MOG in bone-marrow macrophages derived from both FcRgamma+/+ and FcRgamma-/- mice, while MOG-immunoglobulin (Ig)G immune complexes were only internalized by FcRgamma+/+ macrophages. This was associated with cellular activation in FcRgamma+/+ but not FcRgamma-/- macrophages, as assessed by the activation of intracellular mitogen activated protein (MAP)-kinase signalling elements. We propose that protection from EAE in FcRgamma-deficient mice is due to the inefficient antigen processing/presentation of myelin proteins during the induction of secondary immune responses locally in the CNS, which leads to demyelination. This demonstrates the importance of FcR in the promotion of **autoimmune inflammation** of the CNS and highlights the **therapeutic** possibility of **treatment** of MS with **FcR** -directed modalities.

5/7/40 (Item 40 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

0011799046 BIOSIS NO.: 199900058706
FcR-mediated **inhibition** of cell activation and other forms of coinhibition
AUTHOR: Anderson Colin C; Sinclair Nicholas R S (Reprint)
AUTHOR ADDRESS: Dep. Microbiol. Immunol., Univ. Western Ontario, London, Ontario N6A 5C1, Canada**Canada
JOURNAL: Critical Reviews in Immunology 18 (6): p525-544 1998 1998
MEDIUM: print
ISSN: 1040-8401
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Citation
LANGUAGE: English

5/7/65 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

13420020 EMBASE No: 2005478653
Regulation of allergy by Fc receptors
Bruhns P.; Fremont S.; Daeron M.
M. Daeron, Unite d'Allergologie Moleculaire et Cellulaire, Departement d'Immunologie, Institut Pasteur, 25 rue du Docteur Roux, 75015 Paris France
AUTHOR EMAIL: daeron@pasteur.fr
Current Opinion in Immunology (CURR. OPIN. IMMUNOL.) (United Kingdom) 2005, 17/6 (662-669)
CODEN: COPIE ISSN: 0952-7915
PUBLISHER ITEM IDENTIFIER: S0952791505001615
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

The aggregation of high-affinity IgE receptors (FcepsilonRI) on mast cells and basophils has long been known as the critical event that initiates allergic reactions. Monomeric IgE was recently found to induce a variety of effects when binding to FcepsilonRI. Upregulation of FcepsilonRI only requires binding, whereas other responses require FcepsilonRI aggregation. Interestingly, FcepsilonRI aggregation has recently been understood to generate a mixture of positive and negative intracellular signals. Mast cells and basophils also express low-affinity and, under specific conditions, high-affinity IgG receptors. When co-engaging these receptors with FcepsilonRI, IgG antibodies can amplify or dampen IgE-induced mast cell activation. On the basis of these findings, it has been proposed that **FcRs** can be used as targets and/or tools for new ***therapeutic*** approaches to allergies. (c) 2005 Elsevier Ltd. All rights reserved.

5/7/70 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE

12322778 EMBASE No: 2003437176
Roles of Fc receptors in **autoimmunity**
Takai T.
T. Takai, Dept. of Experimental Immunology, Inst. of Development, Ageing/Cancer, Tohoku University, Seiryo 4-1, Sendai 980-8575 Japan
AUTHOR EMAIL: tostakai@idac.tohoku.ac.jp
Nature Reviews Immunology (NAT. REV. IMMUNOL.) (United Kingdom) 2002, 2/8 (580-592)
CODEN: NRIAB ISSN: 1474-1733
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 121

The receptors for the Fc of immunoglobulins, Fc receptors (FcRs), link the humoral and cellular branches of the immune system, and they have important functions in the activation and down-modulation of immune responses. Balanced signalling through activating and ***inhibitory*** ***FcRs*** regulates the activity of various cells in the immune system. Recent work in animal models indicates that the development of many human **autoimmune** diseases might be caused by impairment of the FcR regulatory system. This ***review*** provides an overview of the mechanisms of FcR-based immune regulation and describes how **autoimmune** disease might result from its dysfunction.

5/7/77 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

11404464 EMBASE No: 2001412085
Receptor modulation by FcgammaRI-specific fusion proteins is dependent on receptor number and modified by IgG
Guyre C.A.; Keler T.; Swink S.L.; Vitale L.A.; Graziano R.F.; Fanger M.W.
Dr. M.W. Fanger, Department of Microbiology, Dartmouth Medical School, 1 Medical Center Drive, Lebanon, NH 03756 United States
AUTHOR EMAIL: Michael.W.Fanger@Dartmouth.edu
Journal of Immunology (J. IMMUNOL.) (United States) 01 DEC 2001, 167/11 (6303-6311)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal ; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 41

The high-affinity IgG receptor, FcgammaRI (CD64), is constitutively expressed exclusively on professional APCs. Human FcgammaRI binds monomeric IgG with high affinity and is, therefore, saturated in vivo. The binding of IgG to FcgammaRI causes receptor recycling, while Abs that cross-link FcgammaRI cause rapid down-modulation of surface FcgammaRI. Because studies performed in the absence of ligand may not be representative of FcgammaRI modulation in vivo, we investigated the ability of FcgammaRI-cross-linking Abs and non-cross-linking derivatives to modulate FcgammaRI in the presence and absence of ligand. In the absence of ligand mAb H22 and wH22xeGFP, an enhanced green fluorescent protein (eGFP)-labeled fusion protein of H22, cross-linked and rapidly down-modulated surface FcgammaRI on the human myeloid cell line, U937, and its high FcgammaRI-expressing subclone, 10.6. This effect was dependent on the concentration of fusion protein and the level of FcgammaRI expression and correlated with internalization of both wH22xeGFP and FcgammaRI, itself, as assessed by confocal microscopy. A single-chain Fv version, sFv22xeGFP, which does not cross-link FcgammaRI, was unable to modulate FcgammaRI in the absence of IgG. However, if ligand was present, treatment with either monovalent or cross-linking fusion protein led to intracellular receptor accumulation. These findings suggest at least two alternate mechanisms of internalization that are influenced by ligand and demonstrate the physiologic potential of FcgammaRI to transport a large antigenic load into APCs for processing. These studies may lead to the development of better FcgammaRI-targeted vaccines, as well as **therapies** to down-modulate **FcR** involved in **autoimmune** diseases.

5/7/78 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

11138266 EMBASE No: 2001154630
IgG Fc receptors
Ravetch J.V.; Bolland S.
J.V. Ravetch, Laboratory of Molecular Genetics, Rockefeller University,

1230 York Ave, New York, NY 10021 United States
AUTHOR EMAIL: ravetch@rockefeller.edu
Annual Review of Immunology (ANNU. REV. IMMUNOL.) (United States)
2001, 19/- (275-290)
CODEN: ARIMD ISSN: 0732-0582
DOCUMENT TYPE: Journal ; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 98

Since the description of the first mouse knockout for an IgG Fc receptor seven years ago, considerable progress has been made in defining the in vivo functions of these receptors in diverse biological systems. The role of activating FcgammaRs in providing a critical link between ligands and effector cells in type II and type III **inflammation** is now well established and has led to a fundamental revision of the significance of these receptors in initiating cellular responses in host defense, in determining the efficacy of therapeutic antibodies, and in pathological ***autoimmune*** conditions. Considerable progress has been made in the last two years on the in vivo regulation of these responses, through the appreciation of the importance of balancing activation responses with ***inhibitory*** signaling. The ***inhibitory*** ***FcR*** functions in the maintenance of peripheral tolerance, in regulating the threshold of activation responses, and ultimately in terminating IgG mediated effector stimulation. The consequences of deleting the inhibitory arm of this system are thus manifested in both the afferent and efferent immune responses. The hyperresponsive state that results leads to greatly magnified effector responses by cytotoxic antibodies and immune complexes and can culminate in **autoimmunity** and **autoimmune** disease when modified by environmental or genetic factors. Fcgamma Rs offer a paradigm for the biological significance of balancing activation and inhibitory signaling in the expanding family of activation/inhibitory receptor pairs found in the immune system.

5/7/82 (Item 21 from file: 73)
DIALOG(R)File 73:EMBASE

10739534 EMBASE No: 2000219885
Immune complex and Fc receptor-mediated augmentation of antigen presentation for in vivo Th cell responses
Hamano Y.; Arase H.; Saisho H.; Saito T.
Dr. T. Saito, Department of Molecular Genetics, Chiba Univ. Grad. School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670 Japan
AUTHOR EMAIL: saito@med.m.chiba-u.ac.jp
Journal of Immunology (J. IMMUNOL.) (United States) 15 JUN 2000, 164/12 (6113-6119)
CODEN: JOIMA ISSN: 0022-1767
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 34

It has recently been established that FcRs are involved in the triggering of type II and III ***inflammatory*** responses. Although FcR is not believed to be involved in the regulation of T cell function, the in vivo contribution of FcRs to T cell function still remains unclear. We analyzed in vivo responses of delayed-type hypersensitivity and proliferation of CD4sup + T cells to Ags in FcRgamma(-/-) mice lacking the expression and function of FcgammaRI, FcgammaRIII, and FcepsilonRI. We found that the delayed-type hypersensitivity response in FcRgamma(-/-) mice is significantly decreased compared with that in wild-type mice. Moreover, the secondary responses of proliferation and cytokine production as well as the Ab formation by CD4sup + T cells from FcRgamma(- /-) mice to Ag and normal APCs were also reduced. In contrast, in vitro primary T cell proliferative responses upon stimulation with anti-TCR Ab or MLR as well as in vivo primary response against staphylococcus enterotoxin B **administration** were not different between T cells from **FcRgamma**(-/-) and wild- type

mice. In addition, the Ag presentation function of APCs from unimmunized FcRgamma(-/-) mice was normal. On the other hand, Ab-deficient mice also revealed impaired T cell responses. These results demonstrate that the defective T cell responses in FcRgamma(-/-) mice were due to impaired Ag presentation during in vivo priming not to a defect in T cells. Therefore, they suggest that the FcRs on APCs mediate efficient priming of Th cell responses in vivo in an immune complex-dependent manner.

5/7/84 (Item 23 from file: 73)
DIALOG(R)File 73:EMBASE

07567363 EMBASE No: 1999036035
Modulation of immune complex-induced **inflammation** in vivo by the coordinate expression of activation and inhibitory Fc receptors
Clynes R.; Maizes J.S.; Guinamard R.; Ono M.; Takai T.; Ravetch J.V.
J.V. Ravetch, Lab. of Molec. Genetics/Immunology, Rockefeller University, 1230 York Ave., New York, NY 10021 United States
AUTHOR EMAIL: ravetch@rockvax.rockefeller.edu
Journal of Experimental Medicine (J. EXP. MED.) (United States) 04 JAN 1999, 189/1 (179-185)
CODEN: JEMEA ISSN: 0022-1007
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 40

Autoantibodies and immune complexes are major pathogenic factors in **autoimmune** injury, responsible for initiation of the ***inflammatory*** cascade and its resulting tissue damage. This activation results from the interaction of immunoglobulin (Ig)G Fc receptors containing an activation motif (ITAM) with immune complexes (ICs) and cytotoxic autoantibodies which initiates and propagates an ***inflammatory*** response. In vitro, this pathway can be interrupted by coligation to FcgammaRIIB, an IgG Fc receptor containing an inhibitory motif (ITIM). In this report, we describe the in vivo consequences of FcgammaRII deficiency in the **inflammatory** response using a mouse model of IC alveolitis. At subthreshold concentrations of ICs that fail to elicit **inflammatory** responses in wild-type mice, FcgammaRII-deficient mice developed robust **inflammatory** responses characterized by increased hemorrhage, edema, and neutrophil infiltration. Bronchoalveolar fluids from FcgammaRII(-/-) stimulated mice contain higher levels of tumor necrosis factor and chemotactic activity, suggesting that FcgammaRII deficiency lowers the threshold of IC stimulation of resident cells such as the alveolar macrophage. In contrast, complement- and complement receptor-deficient mice develop normal **inflammatory** responses to suprathreshold levels of ICs, while **FcRgamma**(-/-) mice are completely protected from ***inflammatory*** injury. An ***inhibitory*** role for FcgammaRII on macrophages is demonstrated by analysis of FcgammaRII(-/-) macrophages which show greater phagocytic and calcium flux responses upon FcgammaRIII engagement. These data reveal contrasting roles for the cellular receptors for IgG on **inflammatory** cells, providing a regulatory mechanism for setting thresholds for IC sensitivity based on the ratio of ITIM to ITAM FcgammaR expression. Exploiting the FcgammaRII inhibitory pathway could thus provide a new therapeutic approach for modulating antibody-triggered ***inflammation*** .

5/7/86 (Item 25 from file: 73)
DIALOG(R)File 73:EMBASE

06836215 EMBASE No: 1997118721
Fc receptor biology
Daeron M.
M. Daeron, LICC, INSERM U.255, Institut Curie, 26 rue d'Ulm, 75005 Paris France

AUTHOR EMAIL: Marc.Daeron@curie.fr
Annual Review of Immunology (ANNU. REV. IMMUNOL.) (United States) 1997
, 15/- (203-234)
CODEN: ARIMD ISSN: 0732-0582
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 198

This **review** deals with membrane Fc receptors (FcR) of the immunoglobulin superfamily. It is focused on the mechanisms by which FcR trigger and regulate biological responses of cells on which they are expressed. FcR deliver signals when they are aggregated at the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and syk family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell activation, endocytosis, and phagocytosis. The nature of responses depends primarily on the cell type. The aggregation of FcR without ITAM does not trigger cell activation. Most of these FcR internalize their ligands, which can be endocytosed, phagocytosed, or transcytosed. The fate of internalized receptor-ligand complexes depends on defined sequences in the intracytoplasmic domain of the receptors. The coaggregation of different FcR results in positive or negative cooperation. Some FcR without ITAM use FcR with ITAM as signal transduction subunits. The coaggregation of antigen receptors or of **FcR** having ITAMs with **FcR** having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. ***FcR*** therefore appear as the subunits of multichain receptors whose constitution is not predetermined and which deliver adaptative messages as a function of the environment.

5/7/88 (Item 27 from file: 73)
DIALOG(R)File 73:EMBASE

04840739 EMBASE No: 1991335475
Fc receptors and immunoglobulin binding factors
Fridman W.H.
Lab. d'Immunologie Cell./Clin., INSERM U.255, Institut Curie, 26 rue d'Ulm,75231 Paris-cedex 05 France
FASEB Journal (FASEB J.) (United States) 1991, 5/12 (2684-2690)
CODEN: FAJOE ISSN: 0892-6638
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Receptors for the Fc portion of Ig (Fc receptors, FcR) are found on all cell types of the immune system. Three types of FcR react with IgG: FcgammaRI is a high-affinity receptor binding IgG monomers whereas FcgammaRII and FcgammaRIII are low-affinity receptors binding IgG immune complexes; the three types of FcgammaR are members of the Ig superfamily. Two FcR react with IgE: FcepsilonRI is a multichain receptor binding IgE with high affinity; it is composed of an IgE-binding alpha chain, homologous to FcgammaRIII, and of gamma and beta chains that are necessary for receptor expression and signal transduction. The low-affinity FcepsilonRII is the only FcR described so far that is not a member of the Ig superfamily but resembles animal lectins; it is composed of a transmembrane chain with an intracytoplasmic NHinf 2 terminus. FcalphaR has homology with FcgammaR and is a member of the Ig superfamily. Receptors for IgM and IgD are not characterized yet. Finally, Ig transport is made by FcR-like molecules such as the poly-Ig receptor or an MHC-like receptor found on neonatal intestine. A remarkable property of most FcR is the fact that they are released in cell supernatants and circulate in biological fluids as immunoglobulin binding factors (IBF) generated either by cleavage at the cell membrane or by splicing of FcR transmembrane exon. Immunoglobulin binding factors may interfere with Ig-mediated functions and have direct immunoregulatory activities. Involvement of FcR or IBF has been

postulated in several diseases, and monoclonal antibodies to **FcR** are beginning to be used in **therapeutics**, particularly to target cytotoxic effector lymphocytes and monocytes to tumor cells.

5/7/94 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

19677665 PMID: 16186811
Engineering the Fc region of immunoglobulin G to modulate in vivo antibody levels.
Vaccaro Carlos; Zhou Jinchun; Ober Raimund J; Ward E Sally
Center for Immunology, University of Texas Southwestern Medical Center, 6000 Harry Hines Blvd., Dallas, Texas 75390-9093, USA.
Nature biotechnology (United States) Oct 2005, 23 (10) p1283-8, ISSN 1087-0156--Print Journal Code: 9604648
Contract/Grant No.: R01 AI 39167; AI; NIAID; R01 AI 50747; AI; NIAID; R01 AI 55556; AI; NIAID
Publishing Model Print-Electronic; Comment in Nat Biotechnol. 2005 Oct;23(10) 1232-4; Comment in PMID 16211062
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
We have engineered the Fc region of a human immunoglobulin G (IgG) to generate a mutated antibody that modulates the concentrations of endogenous IgGs in vivo. This has been achieved by targeting the activity of the Fc receptor, FcRn, which serves through its IgG salvage function to maintain and regulate IgG concentrations in the body. We show that an IgG whose Fc region was engineered to bind with higher affinity and reduced pH dependence to **FcRn** potently **inhibits** **FcRn** -IgG interactions and induces a rapid decrease of IgG levels in mice. Such FcRn blockers (or 'Abdegs,' for antibodies that enhance IgG degradation) may have uses in reducing IgG levels in antibody-mediated diseases and in inducing the rapid clearance of IgG-toxin or IgG-drug complexes.
Record Date Created: 20051007
Record Date Completed: 20060105
Date of Electronic Publication: 20050925

5/7/115 (Item 13 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

137001511 CA: 137(1)1511b PATENT
FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
INVENTOR(AUTHOR): Roopenian, Derry
LOCATION: USA
ASSIGNEE: The Jackson Laboratory
PATENT: PCT International ; WO 200243658 A2 DATE: 20020606
APPLICATION: WO 2001US44166 (20011106) *US PV246207 (20001106) *US PV266649 (20010206)
PAGES: 74 pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
CLASS: A61K-000/A
DESIGNATED COUNTRIES: CA; JP DESIGNATED REGIONAL: AT; BE; CH; CY; DE; DK ; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; TR
SECTION:
CA203002 Biochemical Genetics
CA214XXX Mammalian Pathological Biochemistry
CA215XXX Immunochemistry
IDENTIFIERS: FcRn gene knockout mouse IgG catabolism model autoimmune disease
DESCRIPTORS:
Drug delivery systems...

aerosols; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Blood vessel,disease... Skin,disease...
dermal vasculitis; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Staining,biological...
detecting FcRn with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Pharmacokinetics...
detg.; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Immunoassay...
enzyme-linked immunosorbent assay, detecting FcRn with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Intestine... Lung... Nose...
epithelium, drug delivery through; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Mouse... Disease models... Autoimmune disease... Lupus erythematosus...
Myasthenia gravis... Rheumatoid arthritis... Sjogren's syndrome... Drug screening...
FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Newborn...
FcRn-mediated drug delivery in; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Embryo,animal...
fetus, FcRn-mediated drug delivery in; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Cytometry...
flow, detecting FcRn with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Immunoglobulins...
fragments, Fc, candidate agent for drug delivery; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Immunoglobulins...
G; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Globulins,biological studies...
γ-, hypergammaglobulinemia, diseases pptd. by, therapy for; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Gene targeting...
gene knockout; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Kidney,disease...
Goodpasture's syndrome; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Immunoglobulins...
G1; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Antisense oligonucleotides...
inhibitor of FcRn mediated IgG protection; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Diabetes mellitus...
insulin-resistant; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Blood vessel,disease...
Kawasaki; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Antibodies...
monoclonal; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Drug delivery systems...
mucosal; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases

Immunoglobulin receptors...
    neonatal; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Gene,microbial...
    neoR, replacing FcRn gene with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Drug delivery systems...
    oral; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Skin,disease...
    pemphigus vulgaris; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Artery,disease...
    periarteritis nodosa; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Hybridoma...
    producing mAb; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Immunoassay...
    radioimmunoassay, detecting FcRn with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Drug delivery systems...
    screening candidate agent for; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Lupus erythematosus...
    systemic; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Drug delivery systems...
    transdermal; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases
Antibodies...
    use in lateral flow assay, detecting FcRn with; FcRn gene knockout mouse showing increased IgG catabolism as models for autoimmune diseases

5/7/119 (Item 17 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

129301314 CA: 129(23)301314e JOURNAL
Fc-dependent immune regulation. Enhancement and/suppression directed by antibody-engaging functional Fc receptors (FcR)
AUTHOR(S): Bell, Clara G. H.
LOCATION: UIC. Col. Med., Micro./Immunol. M/C 790, Chicago, IL, 60612, USA
JOURNAL: Biochem. Soc. Trans. DATE: 1998 VOLUME: 26 NUMBER: 3 PAGES: S200 CODEN: BCSTB5 ISSN: 0300-5127 LANGUAGE: English PUBLISHER: Portland Press Ltd.
SECTION:
CA215000 Immunochemistry
IDENTIFIERS: Fc receptor immune regulation antibody review
DESCRIPTORS:
Antibodies... Fc receptors... Immunostimulation... Immunosuppression... Signal transduction(biological)...
    immunostimulation vs. immunosuppression directed by antibody-engaging functional Fc receptors
? ds

Set	Items	Description
S1	5	FCR? AND (ALS OR AMYOTROPHIC)
S2	3	RD S1 (unique items)
S3	1858	FCR? (10N)(TREAT? OR THERAP? OR ADMINIST? OR PREVENT? OR INHIBIT? OR SUPPRESS? OR ANTAGONI?)
S4	219	S3 AND (REVIEW? OR INFLAMMAT? OR AUTOIMMUN?)
S5	123	RD S4 (unique items)

?